UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/609,233	06/27/2003	Imtiaz Chaudry	048765/277090	8210

826 7590 04/04/2008

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
HAGHIGHATIAN, MINA	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
04/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/609,233	CHAUDRY, IMTIAZ	
	Examiner	Art Unit	
	MINA HAGHIGHATIAN	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/19/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,12-16,21,25-30,32,34,38-40,51-55,57-64 and 66-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 12-16, 21, 25-30, 32, 34, 38-40, 51-55, 57-64 and 66-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Amendments and Remarks filed on 12/19/07. Claims 1, 38 and 51 have been amended, claims 3-4, 6-11, 17-20, 22-24, 31, 33, 35-37, 41-55 and 65 have been cancelled and no new claims have been added. Accordingly, claims **1, 2, 5, 12-16, 21, 25-30, 32, 34, 38-40, 51-55, 57-64 and 66-69** are under examination.

Objections

The disclosure is objected to because of the following informalities: The specification does not recite the specific concentration range of 0.1 mg/ml to 15 mg/ml. While Applicant has indicated that the said range was present in original claim 4 (now cancelled), the range should be inserted in the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims **1, 2, 5, 12-16, 21, 25-30, 32, 34, 38-40, 51-55, 57-64, 67-69** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 10, 27, 38, 51 recite concentration ranges for the active agents that have no support in the specification. Specification, on pages 14-16 recite various concentration ranges, however there is no mention of 1 mg/ml to 10 mg/ml or 0.15 mg/ml to 15 mg/ml as suitable ranges. In fact concentrations of 0.1 mg/ml and 0.15 mg/ml are not listed at all and 1 mg/ml is only cited as an upper limit and not a lower limit.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 12-14, 16 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Kiechel et al (4,885,305).

Kiechel discloses nasal compositions comprising as active agent a calcium antagonist together with a non-toxic pharmaceutically acceptable nasal carrier therefor (see abstract). Preferred calcium antagonists include **felodipine, fluordipine, nicardipine, nifedipine,** etc. Most preferred is nicardipine (see col. 1, lines 60-67)

The composition is preferably in the form of an aqueous solution. Alternatively it may be in the form of a **suspension** or an **emulsion** (col. 2, lines 20-25). The said formulations may also comprise pharmaceutical excipients such as anti-oxidants, **preservatives** (conservation agents), etc. Such excipients include sodium benzoate, benzalkonium chloride, etc (see col. 2, lines 32-54). It is preferred to administer a nasal spray which is **isotonic** with respect to the ciliary mucus (col. 2, lines 60-68).

The formulations are said to have a **pH** of between 3.5 and 9, and preferably from **3 to 4**. The desired pH may be achieved by means of the presence of a buffer system, e.g. acetic acid/sodium acetate, etc (see col. 3, lines 1-13). The said formulations are sterilized under conventional conditions and packaged in conventional manner in a nasal applicator adapted to produce a spray of the composition. The formulation may be packaged in unit doses in ampoules (see col. 3, lines 14-35). The formulation has a suitable concentration range of the active agent from about 0.1 to about 0.45% or 1 to 4.5 mg/ml (see col. 3, lines 43-59). The nasal formulations taught

by Kiechel are said to be useful for the same indications as the systemic administration, i.e. cardiac disorders, **hypertension**, etc (col. 3, lines 61-67).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 15, 25-26, 38-40, 51-55, 57-60, 66-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kiechel et al (4,885,305) in view of Mead et al (6,608,054).

Kiechel et al discussed above lacks disclosure on adding complexing agents.

Mead et al teach pharmaceutical compositions based on anticholinergics and endothelin antagonists, processes for preparing them and their use in the treatment of respiratory tract disease (see abstract). The said disorders include **pulmonary hypertension** (see col. 2, lines 56-64). Mead discloses that the formulation preferably have a **pH of from 2 to 7**, which is obtained by addition of acids or a mixture of acids. Preferably acids which have other properties in addition to their acidifying qualities, e.g. complexing agent, antioxidant, etc. The addition of editic acid (EDTA) or one of the known salts thereof, sodium edentate, as stabilizer or complexing agents is unnecessary. Other embodiments may contain this compound or these compounds. In

a preferred embodiment the content based on sodium edetate is less than 100mg/100ml. Generally, inhalable solutions in which the content of **sodium edetate** is from 0 to 10mg/ml are preferred (col. 9, lines 1-35). Preferred formulations contain, in addition to the solvent water and the combination of active substances, only benzalkonium chloride and sodium edetate (col. 10, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Kiechel et al on spray formulations comprising active agents and carriers packaged in unit doses for treating disorders such as hypertension with the teachings of Mead et al on inhalable formulations comprising active agents, carriers and complexing agents with reasonable expectations of successfully preparing safe, stable formulations for effective inhalation therapy. In other words, **all** the claimed elements were known in the prior art and one skilled in the art **could have** combined the elements as claimed by known methods with no change in their respective functions, and the **combination would have yielded predictable results** to one of ordinary skill in the art at the time of the invention.

Claim 1, 2, 5, 12-16, 21, 25-30, 32, 34, 38-40, 51-55, 57-64 and 66-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (5,554,610) in view of Schwarz (US 20010031738) and further in view of Mead et al (6,608,054).

Williams teaches a **method for the treatment** of **pulmonary hypertension** comprising administering to a mammal an effective amount of a vasodilator. The formulations can treat primary and secondary pulmonary hypertensions (col. 2, lines 1-6). The administration is preferably **through inhalation**. **Unit doses** comprising 0.01 to 50 mg and preferably from 0.1 to 10 mg of the compound are normally administered one to 4 times a day. The compositions are prepared by admixture and can be in a solution or **suspension** form (col. 2, lines 16-48, 60-67). One preferred composition comprises in an **aqueous suspension** form, additives such as suspending agents, preservatives, carriers and **buffers**. The said agents include **propylene glycol**, **ethyl alcohol,** etc. The compositions for administration to the respiratory tract are presented as snuff or an **aerosol** or **solution** for a **nebulizer** or as a microfine powder for insufflation, alone or in combination with an inert carrier. In other preparations, such as for parenteral administration, the fluid unit dose forms are prepared containing the compound and a **sterile** vehicle, undergo **filter sterilization** and filled into a vial. The compositions are typically accompanied by written or printed directions for use (see col. 3, lines 1-66).

Williams also discloses that suitable vasodilators include **calcium channel blockers** such as **nifedipine** (col. 4, lines 20-21). A particularly favored pharmaceutically acceptable composition is an inhalation composition, suitably in unit dosage form (col. 4, lines 37-40). Williams lacks disclosure on pH levels, isotonicity of the formulations and addition of complexing agents.

Schwarz teaches a method of treating **pulmonary hypertension by inhalation**. It is discloses that the aerosol **suspensions** can be aerosolized by a metered dose inhaler ([0049]) or with a pressure-driven **aerosol nebulizer** or an **ultrasonic nebulizer**. The suitable carrier is typically water and most preferably **sterile** water, and preferably made **isotonic**. Optional preservatives, **pH-adjusting agents**, **buffering** agents and surfactants are included (see [0041] and [0051]). The doses of the active compounds may be provided as **one or several prepackaged units** (see [0059]). It is disclosed that suitable formulations comprise **citrate** or bis/tri buffer (**pH 6**) (see [0045]).

Mead et al, discussed above, discloses formulations for inhalation comprising complexing agents.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented teachings of Schwarz on inhalation of formulation for treating pulmonary hypertension, with the general teachings and formulations of Williams et al and the formulations of Mead et al with a reasonable expectations of successfully preparing efficient and easy to use formulations that treat pulmonary hypertension in patients. In other words Williams et al are teaching the inhalation of vasodilators for treating pulmonary hypertension. Williams et al disclose the use of buffers for their formulations, however, they are silent with regards to specific pH levels and isotonicity of the formulations. It is well known in the art that mucosal

membranes tolerate certain isotonicity and pH levels. It is also well known in the art that pH levels are adjustable by use of acids, bases or buffers. Schwarz have been provided as supportive art showing that it is known in the art that an isotonic formulation having pH levels of 3-8 are suitable for inhalation. Mead et al is also supportive art showing that adding complexing agents to formulations are known. Thus it is clearly shown that all limitations of the instant claims are met by Williams in view of Schwarz and Mead et al or knowledge generally available to one of ordinary skill in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1,2, 5, 12-16, 21, 25-30, 32, 38-40, 51-55, 57-69** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 5-7, 10-14, 16, 21 and 25-26 of copending Application No. 11/316,458 (US 20060104913). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the reference claims. The instant claim 1 and the reference claim 1 both recite an inhalable formulation for the treatment of pulmonary hypertension comprising from 0.1 to 15 mg/ml of a reducing agent such as calcium channel blocker wherein the formulation is free of a compound selected from the group consisting essentially of I) an anti-EMAP II antibody, ii) antisense EMAP II oligonucleotide and iii) EMAP II antagonist and wherein the formulations have a pH of from 3 to 8. The difference is that instant claim 1 contains a further negative proviso wherein the formulation is not a liposome. The remaining claims are also anticipated by the reference claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 12/19/07 have been fully considered but they are not persuasive. Applicant argues that Kiechel is directed to a formulation for nasal delivery and absorption through nasal mucus. Applicant then asserts that Kiechel can not anticipate the claims. This is not persuasive because the instant claims are drawn to an inhalable formulation. Firstly, the term inhalable is in preamble and is not given weight. Secondly, the term inhalable is not a positive recitation but means the formulation is capable of being inhaled. Furthermore, the added limitation "said formulation is suitable for local administration to the lungs" does not narrow the scope of claim and does not obviate the anticipation rejection. Kiechel et al meets each and every patentable limitation of the claims, thus it anticipates the claims.

Applicant argues that Mead reference "does not cure the deficiencies of kiechel discussed above". Applicant continues that "Mead does not teach a formulation including a calcium channel blocker suitable for localized delivery to the lungs such that a systemic effect is circumvented nor the treatment of pulmonary hypertension by administering a formulation including a calcium channel blocker locally to the lungs of a mammal". This is not persuasive because Mead is the supporting or secondary reference, which provides what is lacking in the teachings or disclosure of the primary reference. The primary reference, Kiechel teaches a formulation comprising calcium

channel blockers and that calcium channel blockers treat pulmonary hypertension. In other words, Mead is not required to teach all the limitations of the claims. It would have been obvious to one of ordinary skill in the art to have combined the two references and prepare the formulations of the instant claims.

Applicant argues that "Williams is silent regarding a formulation suitable for localized delivery to the lungs such that a systemic effect is circumvented as recited in claims 1, 27, 38 and 51". This is not persuasive because Williams is NOT silent regarding localized delivery to the lungs and it is implied that systemic effect is achieved. Williams states that active agents such as vasodilators delivered by inhalation treat pulmonary hypertension and right heart failure (see col. 1, lines 23-38). Even if it is argued that pulmonary hypertension can benefit form local effect of a drug administered to the lung, it is not clear how one can assert that heart failure can be treated by anything other than systemic effect when the drug is delivered to the lung. Thus systemic effect has been shown. Williams is repeatedly stating that inhalation is the suitable delivery method for treating pulmonary hypertension. Applicant states that "Williams only teaches aqueous suspension formulations as being "oral liquid preparations –see column 2, line 60-". This is not persuasive because Williams teaches that "the compound is administered in the form of a unit-dose composition, such as a unit dose oral, parenteral or preferably inhaled composition… such compositions are prepared by admixture and are suitably adapted for oral, inhaled or parenteral administration and as such may be in the form of tablets, capsules, oral liquid preparations, powders, injectable and infusible solutions and suspensions" (see col. 2).

It is also disclosed that "preferably, compositions of the compound are presented for administration to the respiratory tract as a snuff or an aerosol or solution for nebulizer, or as microfine powder for insufflation, alone or in combination with an inert carrier (col. 3, lines 11-15). It is taken that one of ordinary skill in the art would be able to deduce that aqueous suspensions are suitable form for inhalation. It is noted again that the instant claims are drawn to an inhalable formulation and the art teaches an aqueous suspension (oral preparation or infusible suspension) that **can be** inhaled.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Patent Examiner
March 28, 2008